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SUPPLEMENT ARTICLE

The 2016 updated WHO classification of lymphoid neoplasias

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KEYWORDS

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1 | INTRODUCTION

The World Health Organization (WHO) is preparing a revised and updated edition of the 2008 classification of tumors of the hematopoietic and lymphoid tissue to be released in 2017.[1] The aim of this revised version of the 4th edition of the WHO classification is to incorporate the new scientific and clinical information to refine diagnostic criteria for previously described lymphomas, in some cases, change nomenclature to convey better the clinical features of the disease, and to introduce newly recognized disease entities. Much has been learned about non-Hodgkin lymphomas (NHL) after the 2008 WHO classification and monograph was published, as a consequence of new information coming from translational and basic research and improved techniques used for routine diagnosis. The list of genetic aberrations that are present in NHL and that are useful either for diagnosis or for understanding the pathogenesis of different diseases has been growing continuously. Some discoveries found using molecular techniques have been rapidly incorporated into daily diagnostic practice such as immunohistochemical stains for SOX11 or BRAF used to help in the diagnosis of mantle cell lymphoma (MCL) or hairy cell leukemia (HCL), respectively. Molecular detection of the recurrent *MYD88* and *RHOA* or *IDH2* mutations are helping to delineate the morphological spectrum of lymphoplasmocytic lymphoma (LPL) and angioimmunoblastic T-cell lymphoma (AITL), respectively. Nevertheless, the prognostic and diagnostic value of mutational analysis in daily practice and its role in targeted therapy remains to be determined. Although the goals of the WHO classification are to identify well-defined entities, as we move forward some challenges in the WHO classification still continue. The borders between some of the disease entities remain ill-defined for example nodular lymphocyte predominant Hodgkin lymphoma with diffuse growth pattern versus T-cell/histiocyte rich large B-cell lymphoma.

The purpose of this review is to highlight the major changes in the revised WHO classification of lymphoid neoplasms and explain the rationale for these changes. This review will focus on the following:

- Small B-cell lymphoid neoplasms
- Diffuse large B-cell lymphoma
- High grade B-cell lymphomas
- Mature T- and NK-cell neoplasms

2 | SMALL B-CELL LYMPHOID NEOPLASMS

Small B-cell lymphomas are composed mainly of small lymphocytes and are often referred as "low-grade" B-cell lymphomas. The WHO classification intentionally does not divide lymphomas by grade, and because they are not necessarily indolent, the preferred name used is "small B-cell lymphomas" (SBL). They include chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma (FL), nodal marginal zone lymphoma (MZL), MALT lymphoma, HCL, LPL, and MCL.[1] The changes in the revised WHO classification are summarized in Table 1.

2.1 | Precursor lesions

Monoclonal B-cell lymphocytosis (MBL) is now divided in "low-count" and "high-count" defined as less than or greater than 0.5×10^9/L CLL cells in peripheral blood (PB). High-count MBL is now recognized as a precursor lesion of CLL/SLL. In FL and MCL, the—*in situ*—lesions have been renamed as "*in situ* neoplasias" to avoid a lymphoma diagnosis. These are considered precursor lesions with relatively low rate of progression.

TABLE 1 Small B-cell neoplasms within the 2008 and the revised 2016 WHO classification

2008 WHO classification	2016 revision	Comments
Chronic lymphocytic leukemia/ Small lymphocytic lymphoma	Chronic lymphocytic leukemia/ Small lymphocytic lymphoma	- defined as >5 × 10^9/L PB CLL cells - *TP53*, *NOTCH1*, *SF3B1*, and *BIRC3* mutations of potential clinical relevance
Monoclonal B-cell lymphocytosis	Monoclonal B-cell lymphocytosis[a] "low count" and "high count"	-low count MBL <0.5 × 10^9/L PB CLL cells -high count MBL >0.5 but <5 × 10^9/L PB CLL cells
B-cell prolymphocytic leukemia	B-cell prolymphocytic leukemia	- no major changes
Splenic marginal zone lymphoma	Splenic marginal zone lymphoma	- no major changes
Hairy cell leukemia	Hairy cell leukemia	- disease-defining mutation, *BRAF* V600E
Splenic diffuse red pulp small B-cell lymphoma	*Splenic diffuse red pulp small B-cell lymphoma*	- no major changes - remains a provisional entity
Hairy cell leukemia-variant	*Hairy cell leukemia-variant*	- *MAP2K1* mutations in 50% the cases
Lymphoplasmacytic lymphoma/ Waldenström macroglobulinemia	Lymphoplasmacytic lymphoma/ Waldenström macroglobulinemia	- disease-defining mutation, *MYD88* L265P - this mutation is not specific for LPL - ~50% of MGUS IgM carry this mutation
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)	- no major changes
Nodal marginal zone lymphoma *-Pediatric marginal zone lymphoma*	Nodal marginal zone lymphoma *-Pediatric marginal zone lymphoma*	- no major changes
Follicular lymphoma (FL)	Follicular lymphoma (FL)	- molecular landscape better understood, *CREBBP*, *EZH2* and *KMT2D* (*MLL2*) possible early driver mutations.
-*in situ* follicular lymphoma	- *in situ* follicular neoplasia[a]	- change in nomenclature. - considered a precursor lesion with low risk of progression.
	- duodenal-type FL[a]	- localized variant with low risk of dissemination
	- predominantly diffuse FL with 1p36 deletion[a]	- new recognized variant, often localized inguinal mass, lacks *BCL2* rearrangement
- *Pediatric FL (variant of FL)*	Pediatric-type FL[a]	- change in nomenclature. - usually occurs in children and young adults, rarely in older individuals. - excellent prognosis even with conservative approach. - recognized as a definite disease entity - frequent *TNFRSF14* and *MAP2K1* mutations
	Large B-cell lymphoma with IRF4 rearrangement[a]	- new provisional entity to distinguish from PTFL and DLBCL - usually occurs in children and young adults - involves mainly Waldeyer ring and cervical lymph nodes
Mantle cell lymphoma	Mantle cell lymphoma	- two MCL subtypes are recognized
- classical MCL	- classical MCL	- mostly unmutated IGHV, mostly SOX11$^+$
	- leukemic non-nodal MCL[a]	- mutated IGHV, SOX11$^-$, PB, BM, and spleen - *TP53* may occur and result in aggressive disease
	- cyclin D1-	- ~ 50% *CCND2* rearrangements
- *in situ* mantle cell lymphoma	- *in situ* mantle cell neoplasia[a]	- change in nomenclature

Provisional entities are written in italics.

[a]Changes in nomenclature or new provisional or definite entities

2.2 | Follicular lymphoma

Follicular lymphoma is clinically and morphologically a rather heterogeneous disease with complex cytogenetic and molecular abnormalities. Several variants are now recognized including duodenal-type FL, a rather localized disorder with low risk of dissemination, and predominantly diffuse FL with 1p36 deletion that often presents as a localized inguinal mass and lacks *BCL2* rearrangement.

2.3 | Pediatric-type FL

Pediatric-type FL (PTFL) is now a definite entity. It has been renamed because similar cases may occur in adults. The criteria for this diagnosis should be strictly applied to avoid misdiagnosis especially with conventional FL grade 3B that is considered a more aggressive disease, and with conventional FL grade 1-2, *BCL2* negative. Pediatric-type FL has excellent prognosis and a conservative watch-and-wait approach is recommended.[3]

2.4 | Large-B-cell lymphoma with *IRF4* rearrangement

Large-B-cell lymphoma with *IRF4* rearrangement is a new provisional entity that most commonly affects children and young adults. It involves mainly the Waldeyer's ring and cervical lymph nodes and is usually low stage disease at presentation. These lymphomas may have a follicular, follicular/diffuse, or diffuse growth pattern. They are characterized by the strong expression of IRF4/MUM1 and BCL6, and approximately 50% of the cases express BCL2 and CD10. Most cases have IGH/*IRF4* rearrangement and *BCL6* alterations (Figure 1). Despite the strong expression of IRF4/MUM1, these cases have a germinal center signature by gene expression profiling (GEP). Most cases have shown good response to chemotherapy.[4]

2.5 | Mantle cell lymphoma

Mantle cell lymphoma usually presents with advanced stage and rapid progression, and historically, it has been considered an aggressive disease. However, now it is recognized that there are 2 pathogenetic ways to develop MCL. The classical MCL orginates from a B cell with unmutated IGHV and expression of SOX11, whereas the leukemic, nonnodal subtype develops from IGHV mutated, SOX11$^-$ B cells. The latter involves mainly PB, bone marrow and spleen. Although these cases have an indolent behaviour, secondary alterations in *TP53* may occur and can result in very aggressive disease.[1]

2.6 | Molecular/cytogenetic changes in SBL

The main changes in SBL are due to the impact of new molecular/cytogenetic information obtained mainly by next generation sequencing. Hairy cell leukemia is defined in almost all cases by the *BRAF* V600E mutation, which is not detected in HCL-variant.[5] In contrast, 50% of HCL-variant carry mutations in *MAP2K1*, which encodes MEK1 downstream of *BRAF*. Another specific genetic alteration found in >90% of LPL/Waldenström macroglobulinemia is *MYD88* L265P mutation.[6] This mutation is also found in 50% of IgM monoclonal gammopathy of undetermined significance, 30% of diffuse large B-cell lymphoma (DLBCL) of nongerminal center type, 50% of primary cutaneous DLBCL, leg type, and rare cases of MZL both splenic and in lymph nodes. It has also been described in 3% of CLL cases defining a specific group of young patients with good prognosis. This mutation is not found in plasma cell myeloma. Another mutation found in 30% of LPL/Waldenström macroglobulinemia and 20% of IgM MGUS is *CXCR4* gene mutation, which seems to impact the clinical presentation and overall survival.

There is a plethora of mutations that are not disease-defining mutations but have prognostic and biological implications. These include *TP53*, *NOTCH1*, *SF3B1*, and *BIRC3* in CLL or *TP53*, *ATM*,

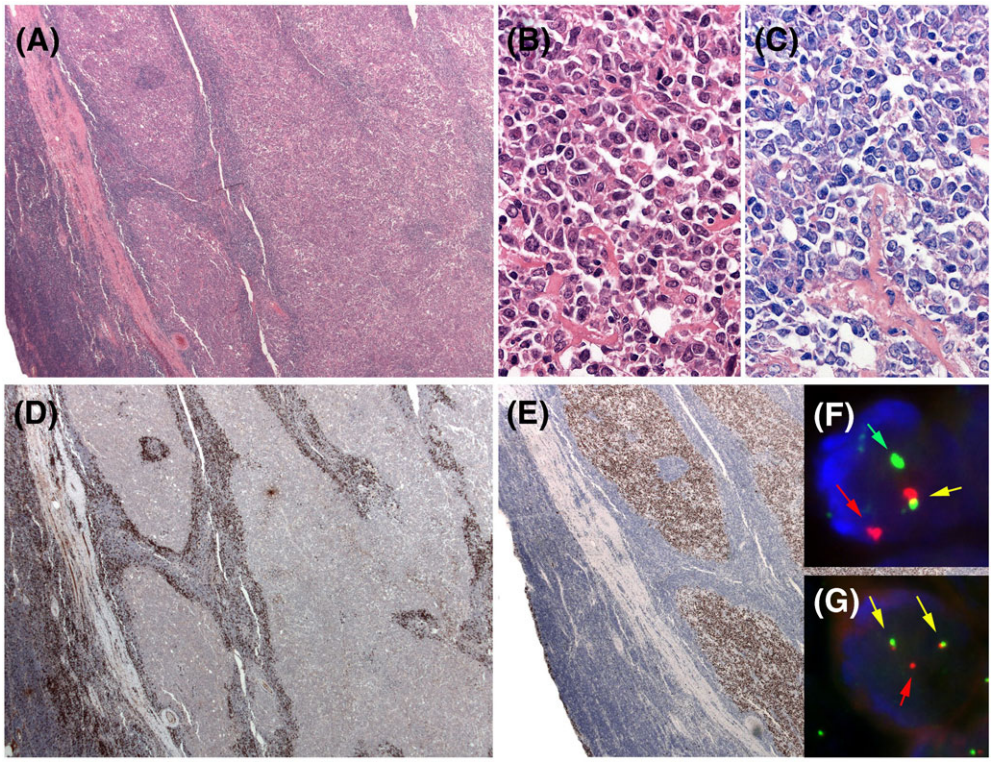

FIGURE 1 Large B-cell lymphoma with *IRF4* rearrangement. A, Lymph node infiltrated by a lymphoma with purely follicular growth pattern. B-C, H&E and Giemsa stain show that the neoplastic follicules are composed of large cells reminiscent of follicular lymphoma grade 3B. D, The IgD stain highlights the attenuated mantle zones and the irregular configuration of the neoplastic follicles. E, IRF4/MUM1 stain is positive in the tumor cells. F, Interphase fluorescence in situ hybridization analysis using an IGH break-apart probe (BAP, Vysis) shows one allele with a normal colocalized signal (yellow arrow) and the second allele with a split red and green signals (red and green arrows) indicating an IGH break. **G,** Interphase FISH analysis using an *IRF4/MUM1* BAP (BAC clones RP3-416 J7, RP5-1077H22 and RP5-856G1) shows 2 alleles with normal colocalized signals (2 yellow arrows), and a third allele with only 1 red signal and loss of the green signal indicating an *IRF4/MUM1* break.

NOTCH 1 and *2* in MCL.[7] In FL, next generation sequencing studies have shown frequent mutations in chromatin regulator/modifier genes.[8] Early driver mutations seem to include mutations in genes such as *CREBBP*, *KMT2D* (*MLL2*), and *EZH2*.

3 | DIFFUSE LARGE B-CELL LYMPHOMA

The 2008 WHO classification of lymphoid malignancies recognizes within the group of DLBCL, several subtypes characterized by unique clinical and pathological features including primary DLBCL of the central nervous system, primary cutaneous DLBCL, leg type, T-cell/histiocyte-rich large cell lymphoma, and EBV positive DLBCL of the elderly. Nevertheless, most cases of DLBCL fall into the "not otherwise specified" (NOS) category.[1] The changes in the revised WHO classification are summarized in Table 2.

3.1 | Cell of origin

On the basis of GEP studies, DLBCLs have been divided into 2 main subgroups; germinal center B cell-like (GCB) and activated B cell-like (ABC)–DLBCL. These molecular subgroups reflect either the stage in B cell development from which the disease originates or the activity of different biological programs. Gene expression profiling, which is considered the gold standard to assign the molecular subtypes, is not routinely available and is not cost-effective in routine diagnosis. Several studies have attempted to recapitulate the molecular subgroups (GCB vs. non-GCB) using a limited panel of antibodies available in most pathology laboratories. The Hans algorithm has been the most widely used in clinical trials. Although most studies have found that immunohistochemical algorithms correlate with prognosis in DLBCL, everybody agrees that these algorithms are an imperfect substitution for GEP.[9] Nevertheless, because of the potential prognostic value of cell of origin and the increasing efforts to tailor therapy on the basis of molecular characteristics of DLBCL, the revised WHO classification requires the identification of these 2 subtypes and the use of immunohistochemistry algorithms is now acceptable.[1]

3.2 | MYC and BCL2 expression

The prognostic importance of simultaneous MYC and BCL2 protein expression, so called "double-expressor" (DE) has been stressed in the revised WHO classification. The recommended cutoff for MYC is >40% positive tumor cells, and the cutoff for BCL2 expression is >50%.[1] MYC and BCL2 DE have been reported to occur in 19-34% of DLBCL patients, and to have a worse prognosis than patients who do not express any or only 1 protein, but better prognosis than double hit (DH) or triple hit (TH) DLBCL (see below), which have a dismal outcome. Interestingly, the DE cases appear more commonly in the ABC subtype, and it has been suggested that this may largely contribute to the known inferior survival of the ABC subtype.[2]

3.3 | EBV$^+$ large B-cell lymphoma

The EBV+ large B-cell lymphoma is now recognized as a definite entity; however, the term "elderly" has been substituted by NOS because these lymphomas can present in younger patients as well. It is important to distinguish this entity from other well-characterized EBV$^+$ lymphomas.[10]

3.4 | EBV+ mucocutaneous ulcer

The EBV+ mucocutaneous ulcer has been added as a new recognized entity and is characterized by a limited growth despite the aggressive morphological features, and good outcome with conservative approach. It is usually associated with iatrogenic immunosuppression and age-related immunosenescence.

3.5 | Burkitt-like lymphoma with 11q aberrations

The Burkitt-like lymphoma with 11q aberrations is a rare disorder that has been added as a provisional entity. Morphologically, these cases resemble Burkitt lymphoma but lack the *MYC* rearrangement. Instead, they have a very characteristic 11q chromosomal alteration with proximal gains and telomeric losses. In contrast to Burkitt lymphoma, they have a more common nodal presentation and broader morphological spectrum; however, they show similar aggressive clinical behaviour.[11]

4 | HIGH-GRADE B-CELL LYMPHOMAS

The morphological distinction between BL and DLBCL has been problematic for pathologists. Gene expression profiling studies have shown that BL has a characteristic signature but that there are cases within the spectrum of DLBCL and aggressive B-cell lymphomas, which have a molecular signature similar to BL or fall into an intermediate category. The 2008 WHO classification recognized this problem an added a provisional category of B cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (BCLU) (Table 2). The *MYC* rearrangements are detected in 30% to 50% of the cases and are usually associated with additional chromosomal aberrations. In this group, the incidence of DH/TH involving *MYC* and *BCL2* and/or *BCL6* has been reported to be high (32%-78%). Because the precise morphological boundaries of this category was not well defined, and therefore, lacked reproducibility among pathologists, it was decided to put all DH/TH in 1 group regardless of the morphology of the tumor cells and designate this group as high-grade B-cell lymphoma with DH/TH rearrangements. Nevertheless, the morphology should be described in the report (DLBCL vs BCLU vs blastoid). The majority of these cases have a GCB phenotype. Cases with high-grade morphology, BCLU or blastoid morophology but which lack *MYC*, *BCL2*, and/or *BCL6* rearrangements should be grouped as high-grade B-cell lymphoma, NOS.[1] High-grade B-cell lymphoma is a disease of older patients presenting with nodal or extranodal disease usually in an advanced clinical stage, high lactate dehydrogenase, and frequent bone marrow and central nervous system infiltration with a dismal prognosis.

TABLE 2 Diffuse large B-cell lymphoma and high-grade B-cell lymphomas within the 2008 and the revised 2016 WHO classification

2008 WHO classification	2016 revision	Comments
Diffuse large B-cell lymphoma (DLBCL), NOS	Diffuse large B-cell lymphoma, NOS	- cell of origin is required. Use of IHC algorithm is acceptable
	- germinal center B-cell type[a] - activated B-cell type[a]	- coexpression of MYC and BCL2 (DE) is prognostically relevant.
T-cell/histocytic rich large B-cell lymphoma	T-cell/histocytic rich large B-cell lymphoma	- no major changes
Primary CNS lymphoma	Primary CNS lymphoma	- frequent *MYD88* L265P mutations
Primary cutaneous DLBCL, leg type	Primary cutaneous DLBCL, leg type	- *MYD88* L265P mutations in ~50% of cases
EBV^+ DLBCL of the elderly	EBV^+ DLBCL, NOS[a]	- change in nomenclature because it occurs also in younger patients - should be distinguished from other well characterized EBV-associated lymphomas
	EBV^+ mucocutaneous ulcer*	- new entity associated with iatrogenic immunosuppression and age-related immunosenescence
DLBCL associated with chronic inflammation	DLBCL associated with chronic inflammation	- no major changes
Lymphomatoid granulomatosis	Lymphomatoid granulomatosis	- no major changes
Primary mediastinal large B-cell lymphoma	Primary mediastinal large B-cell lymphoma	- no major changes
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma	- no major changes
ALK+ large B-cell lymphoma	ALK+ large B-cell lymphoma	- no major changes
Plasmablastic lymphoma	Plasmablastic lymphoma	- MYC rearrangement in ~50% of cases - 70% EBV^+ with latency I or II
Primary effusion lymphoma	Primary effusion lymphoma	- no major changes
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease	HHV8+ DLBCL, NOS[a]	- change in nomenclature
Burkitt lymphoma	Burkitt lymphoma	*TCF3* or *ID3* mutations in up to 70% of cases
	Burkitt-like lymphoma with 11q aberration[a]	-new provisional entity - resembles Burkitt lymphoma but lacks *MYC* translocation
B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma (BCLU)	High grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements[a]	- new category for all double or triple hit lymphomas excluding transformed FL, lymphoblastic lymphoma and MCL
	High grade B-cell lymphoma, NOS[a]	- include cases with BCLU and blastoid morphology without gene rearrangements

Provisional entities are written in italics.

[a]Changes in nomenclature or new provisional or definite entities

TABLE 3 Mature T and NK-cell neoplasms within the 2008 and revised 2016 WHO classification

2008 WHO classification	2016 revision	Comments
T-cell prolymphocytic leukemia	T-cell prolymphocytic leukemia	- no major changes
T-cell large granular lymphocytic leukemias	T-cell large granular lymphocytic leukemias (T-LGL)	- *STAT3* and *STAT5B* mutations in a subset of cases
	Chronic lymphoproliferative disorder (LPD) of NK cells[a]	- new provisional entity - NK-cell counterpart of T-LGL
Aggressive NK-cell leukemia	Aggressive NK-cell leukemia	- no major changes
Systemic EBV$^+$ T cell lymphoproliferative disorder (LPD) of childhood	Systemic EBV$^+$ T cell lymphoma of childhood*	- change in nomenclature due to the fulminant clinical course and monoclonal proliferation - Hemophagocytic syndrome usually present
Hydroa vacciniforme-like lymphoma	Chronic active EBV infection[a] - systemic form - cutaneous form - Hydroa-vacciniforme-like LPD[a] - severe mosquito bite allergy[a]	- new category to encompass the EBV$^+$ T and NK-cell LPD in the pediatric age - can be monoclonal - change in nomenclature. Umbrella term that covers the entire spectrum of the disease - new subgroup.
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma	- no major changes
Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma, nasal type	- no major changes
Enteropathy-associated T-cell lymphoma, type I	Enteropathy-associated T-cell lymphoma	- no major changes
Enteropathy-associated T-cell lymphoma type II	Monomorphic epitheliotropic intestinal T-cell lymphoma[a]	- change in nomenclature - lack association with celiac disease - mostly derived from γδ T cells - *STAT5B* mutations in 36% the cases - recurrent *SETD2* alterations
	Indolent T-cell LPD of the GI tract[a]	- new provisional entity
Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma	- no major changes
Subcutaneous paniculitis-like T-cell lymphoma	Subcutaneous paniculitis-like T-cell lymphoma	- no major changes
Mycosis fungoides	Mycosis fungoides	- no major changes
Sezary syndrome	Sezary syndrome	- no major changes
Primary cutaneous CD30+ LPD - Lymphomatoid papulosis (LyP) - anaplastic large cell lymphoma	Primary cutaneous CD30+ LPD - Lymphomatoid papulosis (LyP) - anaplastic large cell lymphoma	- new morphological subtypes
Primary cutaneous γδ T-cell lymphoma	Primary cutaneous γδ T-cell lymphoma	- needs to be distinguished from other γδ T-cell cutaneous disorders mainly LyP
Primary cutaneous CD8+ aggressive epdermotropic cytotoxic T-cell lymphoma	*Primary cutaneous CD8+ aggressive epdermotropic cytotoxic T-cell lymphoma*	- no major changes - differential diagnosis with LyP type D
	Primary cutaneous acral CD8$^+$ T-cell lymphoma[a]	- new provisional entity
Primary cutaneous CD4+ small/medium T-cell lymphoma	*Primary cutaneous CD4+ small/medium T-cell LPD*[a]	- change in nomenclature. Indolent disorder indistinguishable from clonal drug reactions
Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS	- molecular subgroups recognized
Angioimmunoblastic T-cell lymphoma	Angioimmunoblastic T-cell lymphoma - *Follicular T-cell lymphoma*[a] - *PTCL with TFH phenotype*[a]	- frequent *TET2*, *RHOA* and *IDH2* mutations - new subgroups with THF phenotype

(*Continues*)

TABLE 3 (Continued)

2008 WHO classification	2016 revision	Comments
Anaplastic large cell lymphoma, ALK$^+$	Anaplastic large cell lymphoma, ALK$^+$	- no major changes
Anaplastic large cell lymphoma, ALK$^-$	Anaplastic large cell lymphoma, ALK^{-*}	- definite entity with different subgroups - 6p25 rearrangement (*DUSP22*) subgroup has good prognosis
	Breast implant-associated anaplastic large cell lymphoma[a]	- new provisional entity - the non-invasive disease has good prognosis

Provisional entities are written in italics.

[a]Changes in nomenclature or new provisional or definite entities

4.1 | Fluorescence in situ hybridization

Which cases should be analyzed by fluorescence in situ hybridization (FISH) is a matter of debate. Whether all DLBCL should be analyzed for *MYC*, *BCL2*, and *BCL6* or only those with GCB phenotype or whether to preselect the cases using a 2-step approach (>40% MYC expression, >50% BCL2 expression) should be decided in the different institutions. Nevertheless, only 6% of GCB DLBCL will have DH/TH. Using the 2-step approach will reduce the costs considerably and DH lymphomas missed by this approach will be enriched by cases harbouring *MYC* and *BCL6* and those cases without dual expression, whose clinical significance is unclear.

5 | MATURE T AND NK-CELL NEOPLASMS

Mature T and natural killer cell neoplasms comprise a heterogeneous group of disorders that account for approximately 15% of all NHL. In contrast to B-cell lymphomas, most T-cell lymphomas lack defining genetic alterations, and its classification relies on a combination of morphological and immunophenotypical features.[1] The recognition that T-cell lymphomas are related to the innate and adaptive immune system, as well as enhanced understanding of T-cell subsets such as follicular helper T-cells (TFH) has contributed to improve the classification of T and natural killer cell neoplasms (Table 3). We have learned that the morphological spectrum of AITL is broader than previously thought. The importance of the EBV$^+$ lymphoproliferative disorders of childhood has resulted in the addition of chronic active EBV infection—systemic and cutaneous forms—and changes in nomenclature in the revised 2016 WHO classification.[12] The better understanding of T-cell lymphomas with cutaneous presentation has resulted in new provisional entities—primary cutaneous acral CD8+ T-cell lymphoma—and change in nomenclature in primary cutaneous CD4+ small/medium LPD to stress the indolent behaviour of this disease. Furthermore, in the last years molecular studies have shed light onto the molecular signatures and chromosomal alterations in peripheral T-cell lymphoma (PTCL), NOS. All these findings add increasing evidence that cell lineage is a major determinant in mature T-cell lymphomas biology and help to better delineate established and new entities.

5.1 | Peripheral T-cell lymphoma (PTCL), NOS

Peripheral T-cell lymphoma is a diagnosis of exclusion with broad morphological spectrum presenting mainly as a nodal disease. Gene expression profiling studies have discovered that there are 3 distinct molecular subgroups in PTCL, NOS defined by the overexpression of the transcription factors GATA3 and TBX21 or expression of cytotoxic genes.[13] GATA3 and TBX21 are master regulators of T helper (TH) cells, skewing TH polarization into TH2 and TH1 differentiation pathways, respectively. Importantly, these subgroups have biological and clinical implications. The GATA3 group has an inferior prognosis and overall survival than cases with the TBX21 signature. GATA3 and T-bet antibodies are reliable surrogates to the molecular signatures.

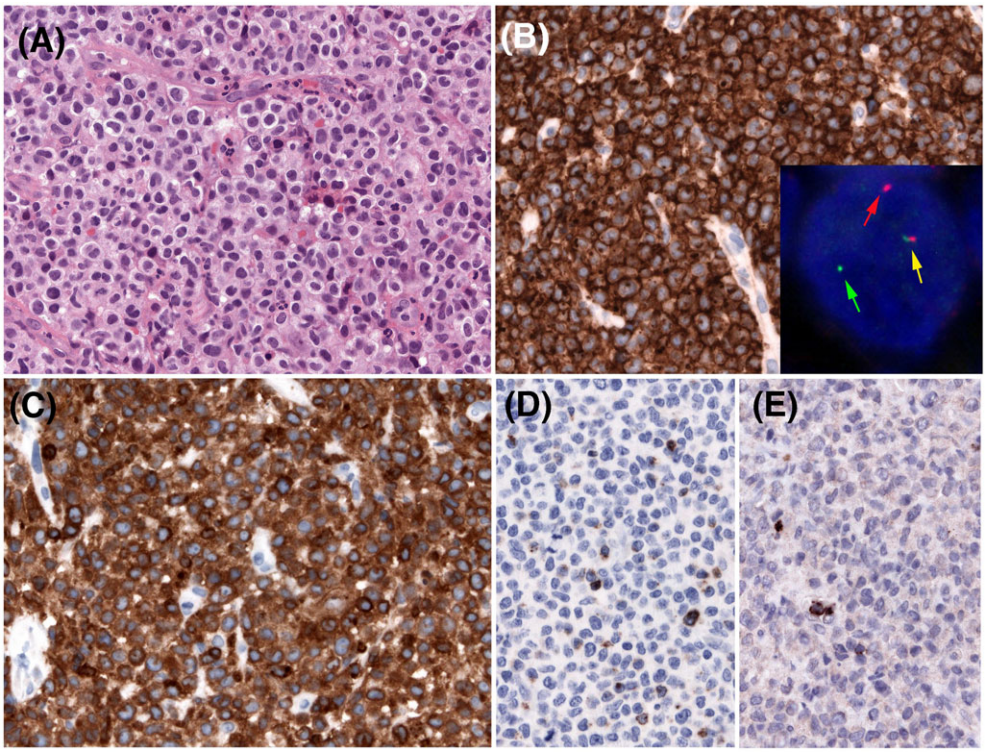

FIGURE 2 **Anaplastic large cell lymphoma, ALK⁻ with a *DUSP22* rearrangement.** A, Lymph node with diffuse infiltration by large lymphoid cells with anaplastic morphology and numerous hallmark cells. B, CD30 is positive in all tumor cells. Insert: interphase FISH analysis using an *IRF4/DUSP22* BAP shows 1 allele with normal colocalized signals (yellow arrow) and the second allele with a split red and green signals(red and green arrow) indicating an *IRF4/DUSP22* break. C, The tumor cells are CD3 positive. D-E, Cytotoxic granules perforin and TIA1 are not expressed in the tumor cells

5.2 | Nodal T-cell lymphomas with TFH phenotype

AITL, the prototype of this group, is characterized by recurrent mutations in *TET2*, *RHOA*, *IDH2*, and *DNMT3A* in a significant proportion of cases.[14] These mutations have been found also in PTCL, NOS with TFH phenotype suggesting that all these lymphomas represent different morphological manifestations of the same disease. Follicular T-cell lymphoma (FTCL) is also included in this group, but often presents with localized disease and less symptoms. For designation of TFH phenotype, at least 2 to 3 TFH-related antigens should be expressed by the tumor cells including ICOS, CXCL13, CD279/PD1, CD10, BCL6, SAP, and CCR5.[1]

5.3 | Anaplastic large-cell lymphomas (ALCL)

In contrast to the 2008 WHO classification, anaplastic large-cell lymphomas (ALCL) ALK⁻ is recognized as a definite entity with different cytogenetic prognostic subgroups.[15] The subgroup with *DUSP22/IRF4* rearrangements on chromosome 6p25 usually lacks cytotoxic granules and seems to have a better prognosis (Figure 2). ALCL ALK⁻ is also associated with breast implants. This subgroup has been incorporated in the revised classification as a provisional entity designated as breast implant–associated ALCL.

5.4 | Primary intestinal T-cell lymphoma

In primary intestinal lymphomas, 2 distinct entities are now recognized; enteropathy-associated T-cell lymphoma (EATL), previously known as EATL type I and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), previously known as EATL type II. MEITL is not associated to celiac disease and is characterized by a monomorphic proliferation of lymphoid cells with CD8 and CD56 expression and mostly derived from γδ T-cells. *STAT5B* mutations were reported in 36% of cases, all with a γδ T-cell phenotype.[16]

6 | CONCLUSIONS

The 2016 revision of the WHO classification maintains the same principles of the 2008 edition, which is to recognize distinct entities on the basis of morphology, immunophenotype, genetic changes, and clinical features. The main changes in this revision include modification in the nomenclature of some diseases mostly to convey better the clinical features of the entity. Lymphoma designation was changed either to "neoplasia" or "lymphoproliferative disorder" to denote either the low risk of progression to a full-blown lymphoma in precursor lesions or to stress the indolent behaviour of the disease, respectively. New provisional entities have been recognized and new scientific and clinical research resulted in upgrading some provisional entities to definite entities. The major contribution of molecular studies that has shed light onto the molecular pathways and chromosomal alterations of many disease entities has also been incorporated.

CONFLICT OF INTEREST

The author have no competing interest.

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